

REMARKS

The Examiner has reopened prosecution as a result of the Applicants' Appeal Brief. Accordingly, the Examiner has provided the following rejections which the Applicants rebut in the following order:

- I. Rejections Under 35 U.S.C. § 102(e)
 - A. Claims 1-6 and 8-14 are rejected as allegedly being anticipated by United States Patent No. 6,821,770 To Hogan et al.
 - B. Claims 1-6 and 8-14 are rejected as allegedly being anticipated by United States Patent No. 6,228,575 To Gingeras et al.
- II. Rejections Under 35 U.S.C. § 103(a)
 - A. Claims 1-5 and 8-13 are rejected as allegedly unpatentable over Kuiper et al, *Current Opinion in Biotechnology* 10:511-516 (199) in view of Greisen et al., *J Clin Microbiol.* 32:335-351 (1994).
 - B. Claims 6 and 14 are rejected as allegedly unpatentable over Kuiper et al, *Current Opinion in Biotechnology* 10:511-516 (199) in view of Greisen et al., *J Clin Microbiol.* 32:335-351 (1994), and in further view of Arfin et al., *J Biol Chem* 275:29672-29684 (2000).
- III. Claims 1 and 3 are rejected under 35 U.S.C. § 112 ¶ 2 as allegedly being indefinite.

I. The Claims Are Not Anticipated

The Examiner has reopened prosecution by providing a new set of anticipatory references. Examiners are obligated to provide the best references at their command. 37 CFR 1.106(b). In this case, the Applicants submit that providing new references under 35 U.S.C. § 102 in response to an Appeal regarding 35 U.S.C. § 103(a) suggests that the Patent Office is not doing a proper job in the first instance. Such an approach creates a hardship on Applicants, particularly academic institutions. Under law, the Patent Office cannot operate in such an arbitrary and capricious manner.

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with either the Hogan et al. or Gingeras et al. references.

A. Hogan et al. Does Not Anticipate The Claims 1-6 and 8-14

The Examiner has pointed to various citations within Hogan et al. in an attempt to find all the Applicants' claimed elements. The Applicants disagree. The Examiner is clearly using hindsight by "picking and choosing" within Hogan et al. disparate information that is not consistent with the overall method taught by Hogan et al.¹ The Examiner has focused on the "what" rather than the "how", and is reminded that the pending claims are method claims and not device claims.

Hogan et al. presents a very complicated method involving the simultaneous assessment of multiple cross-hybridizations (i.e., higher order addresses, intermediate order addresses, and lower order addresses). The Applicants specifically state that the present invention is designed to avoid cross-hybridization assays:

DNA-DNA hybridization methods provide more resolution ... Nonetheless, these methods are not popular, largely due to major disadvantages such as the laborious nature of pairwise cross-hybridizations ...

¹ One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

Applicants' Specification pg 2 ln 16-20. Hogan et al. freely admits that a species determination cannot even be possible until a seventh-level hybridization assessment is performed:

A seventh address representing a collection of species-specific probes can provide information adequate to identify particular species with certainty ... Even though these species represent ... different organisms, it will be apparent that any positive hybridization result with a species-specific probe at the seventh-address must be interpreted in combination with, or in the context of all other results observed at the other addresses in the matrix.

Hogan et al. col 17 ln 31-41 [emphasis added]. Clearly, Hogan et al. requires an integrated systematic method that requires at least seven pair-wise comparisons to even attempt a species identification. Even so, Hogan et al does not guarantee success:

The aggregated collection of positive and negative results from a probe matrix hybridization procedure can be interpreted to provide information about the identity of an organism that is present in the biological sample. ... In many instances, it will be possible to determine the species-level identity of an organism.

Hogan et al. col. 19 ln 13-20. Hogan et al. does not teach a species identification will necessarily happen. Further, the Examiner should realize that (as underlined above) Hogan et al. collects a series of "yes/no" data that is compared to a pre-constructed database (i.e., a look-up table):

Once each hybridization result has been determined to be either positive or negative, the collection of results can be assembled as a profile, a value or a "string" that can be compared with the look-up table stored in a memory device. An exemplary string of results for a four address probe matrix would be (1011) or (+/1/+/+), where "1" or "+" represent positive hybridization results and "0" or "-" represent negative hybridization results.

Hogan et al. col 38 ln 17-23. Hogan et al. teaches a method wherein data collection is limited to the collection of binary information (i.e., does not calculate any signal ratio's) and merely compares linear patterns produced by each address level.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 1 and 9 by reciting "calculating a ratio of said fluorescent target signal to said fluorescent reference signal". This amendment is supported by the Applicants' specification (pg. 6 ln 25-27) and is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

Consequently, Hogan et al. does not anticipate the Applicants' claimed embodiment. The Applicants respectfully request that the Examiner withdraw the present rejection.

B. Gingeras et al. Does Not Anticipate The Claims 1-6 and 8-14

The Examiner has, again, provided a hindsight argument by pointing out isolated elements within Gingeras et al. without considering their integrated use (i.e., Gingeras's methodology). Gingeras et al. clearly describes a repetitive hybridization technique that is dependent upon polymorphisms within a particular sequence:

... each differential hybridization pattern will be associated with a probability of the organism being screened belonging to a particular species (or not) or carrying a particular phenotypic trait (or not). As a result, detection of an increasing number of these sets of differences *allows one to classify the organism* with an increasing level of confidence. ... Therefore, the overall hybridization pattern, which is the aggregate of all the differential hybridizations observed at all regions of the substrate, allows one to assign with high confidence, the speciation and/or phenotype of the organism.

Gingeras et al. col 9 ln 65 - col 10 ln 10 [emphasis added]. Gingeras et al. specifically points out that a single hybridization step will be insufficient to differentiate between a target sequence and a reference sequence:

When a single probe set is being used on the substrate, it will usually not be able to define the differences in sequence between the target and the reference sequence, absent additional knowledge about the target.

Gingeras et al. col 10 ln 11-13 [emphasis]. *Gingeras et al.* does not teach a simple and direct competitive inhibition assay between a labeled reference probe and a labeled target probe:

In general, each nucleotide of interest in the reference sequence requires the same interrogation position in the four sets of probes. Consider, as an example, as reference sequence of 100 nucleotides, 50 of which are of interest, and probes each having a single interrogation position. In this situation, the first probe set requires fifty probes ... the second, third and fourth probe sets ... each also contains a total of fifty probes. The identity of each nucleotide of interest in the reference sequence is determined by comparing the relative hybridization signals at four probes having interrogation positions corresponding to that nucleotide from the four probe sets.

Gingeras et al. col 15 ln 21-35 [emphasis added]. Like Hogan et al., the Applicant has avoided this type of complex repetitive cross-hybridization assay. Further, *Gingeras et al.* does not utilize a hybridization intensity ratio from differentially labeled target/reference probes to determine a species identification.

Consequently, the Applicants submit that *Gingeras et al.* does not anticipate the Applicants' claimed embodiment. The Applicants respectfully request that the Examiner withdraw the present rejection.

II. The Claims Are Not Obvious

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejection does not meet these criteria. The Applicants rebut the establishment of a *prima facie* case of obviousness by the argument below.

A. Claims 1-5 & 8-13 Are Not Obvious Over Kuiper et al & Greisen et al.

1. There Is No Motivation To Combine These Teachings

The Examiner attempts to combine the teachings of two references that one having ordinary skill in the art would not consider related. Kuiper et al. provides a general review in the field of food biotechnology directed at selection processes for bacteria that improve food preservation. The Examiner believes that Kuiper et al. teaches a method to identify bacterial species; it does not:

Of course, specific DNA arrays can be developed for various other purposes, for example, rapid identification of pathogens and spoilage bacteria ...

Kuiper et al. pg. 512, rhc. The Examiner is reminded that “identification” can occur at many levels. Kuiper et al. does not specify what kind of identification is contemplated or what might be involved to differentiate between the various levels of identification. Because Kuiper et al. does not say, the Examiner is not qualified “as one having ordinary skill in the art” to make the determination for Kuiper et al. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (“[T]he examiner's assumptions do not constitute the disclosure of the prior art.”).

On the other hand, Greisen et al. provides a very detailed and sophisticated integration of polymerase chain reaction, gel electrophoresis, DNA sequencing, and “dot blot” hybridization techniques to identify and test primers for amplification of numerous bacterial sequences. Greisen et al. does not provide any detailed description for a method to identify a bacterial species using microarray technologies. The Examiner points to the last paragraph of Greisen et al. as allegedly teaching microarrays:

In a clinical setting, the use of a panel of probes is suited to a detection format ... such as ... a microwell plate ...

Greisen et al. pg. 350. The Federal Circuit has made clear that this type of mere mention only makes something ‘obvious to try’ and does not meet the necessary standards for obviousness. *American Hospital Supply Corp. v. Travenol Laboratories, Inc.*, 745 F.2d 1, 223 USPQ 577 (Fed. Cir. 1984) (“Of course, an ‘obvious to try’ standard is not a

legitimate test of patentability."). In particular, the courts have found that an 'obvious to try' teaching is lacking in specific guidance:

An invention is 'obvious to try' 'where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.'

In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988). Greisen et al. does not discuss the conditions that would be necessary to achieve an effective high-throughput array assay.

Consequently, there are insufficient teachings in both Kuiper et al. and Greisen et al. to substantiate combining their teachings in an attempt to create the Applicant's claimed embodiment.

2. Kuiper et al. And Greisen et al. Fail To Teach All The Claimed Elements

Even if the Examiner believes that Kuiper et al. and Greisen et al. are properly combined (which they are not) a *prima facie* case of obviousness still fails because not all the claimed elements are taught.

The Examiner admits that "Kuiper et al. does not teach the use of at least four strains of reference bacterial species" in the performance of an array high through-put assay. *Office Action* pg. 7. The Examiner then improperly argues that "Greisen et al. teach up to 12 meningitis and contaminant probes (reference and test DNA) tested against seven major bacterial species ... (see page 346 2nd column last two paragraph and Table 4). The Applicants submit that the Examiner is mixing methods. The Examiner's assertion relies on a "Southern blot hybridization" technique (*Greisen et al.*, pg. 346, last paragraph, first sentence) that is not reflected in the Applicants' claimed embodiment.

The Examiner admits that "Greisen et al. does not teach co-hybridizing target and reference DNA in a single step or the use of fluorescence detection for hybridization". *Office Action* pg. 8. The Examiner points to nothing in Kuiper et al. that teaches co-hybridizing a target and reference DNA in a single step.

Further, neither Greisen et al. nor Kuipers et al. teach calculating a ratio of target and reference DNA labels that identifies a bacterial species.

Because, Greisen et al. and Kuipers et al., in combination, do not teach all the Applicant's claimed elements, the Applicants respectfully request that the Examiner withdraw the present rejection.

**3. Kuipers et al. And Greisen et al. Do Not Teach Any
Expectation Of Success**

A reasonable expectation of success has been held to be supported by prior art that explicitly predicts that the process recited in the claims would work.

Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). In the present case, however, the cited references not only do not explicitly predict success for the claimed embodiment, they do not provide any reasonable expectation for success. The claimed embodiment does demonstrate unexpected results when compared to the cited references, thereby obviating the Examiner's obviousness rejection:

There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious.

In re O'Farrell at 903, citing *In re Merck & Co., Inc.*, 800 F.2d 1091, 1098 (Fed. Cir. 1986). As discussed above, none of the references demonstrate the identification of bacterial species using a simple hybridization ratio. Consequently, the Applicants' have demonstrated unexpected results in view of these references.

The Applicants, therefore, respectfully request that the Examiner withdraw the present rejection.

**B. Claims 6 and 14 Not Obvious Over Kuiper et al., Greisen et al., And
Arfin et al.**

The Examiner introduces Arfin et al. against two dependent claims 6, and 14 for teachings related to statistical analysis. Because the above argument and claim amendments clearly place Claims 1 and 9 in condition for allowance the Applicants

submit that Claims 6 and 14 are also not in condition for allowance. Consequently, the Applicants consider this rejection moot.

The Applicants respectfully request that Examiner to withdraw the present rejection.

III. The Claims Are Not Indefinite

The Examiner states that “Claims 3 and 11 [are] rejected as vague and indefinite because the claim fails to further limit claim 1 and 9, respectively”. *Office Action pg. 3*. The Applicants disagree. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 3 and 11 by deleting the term “organism”. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants respectfully request that the Examiner withdraw the present rejection.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

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